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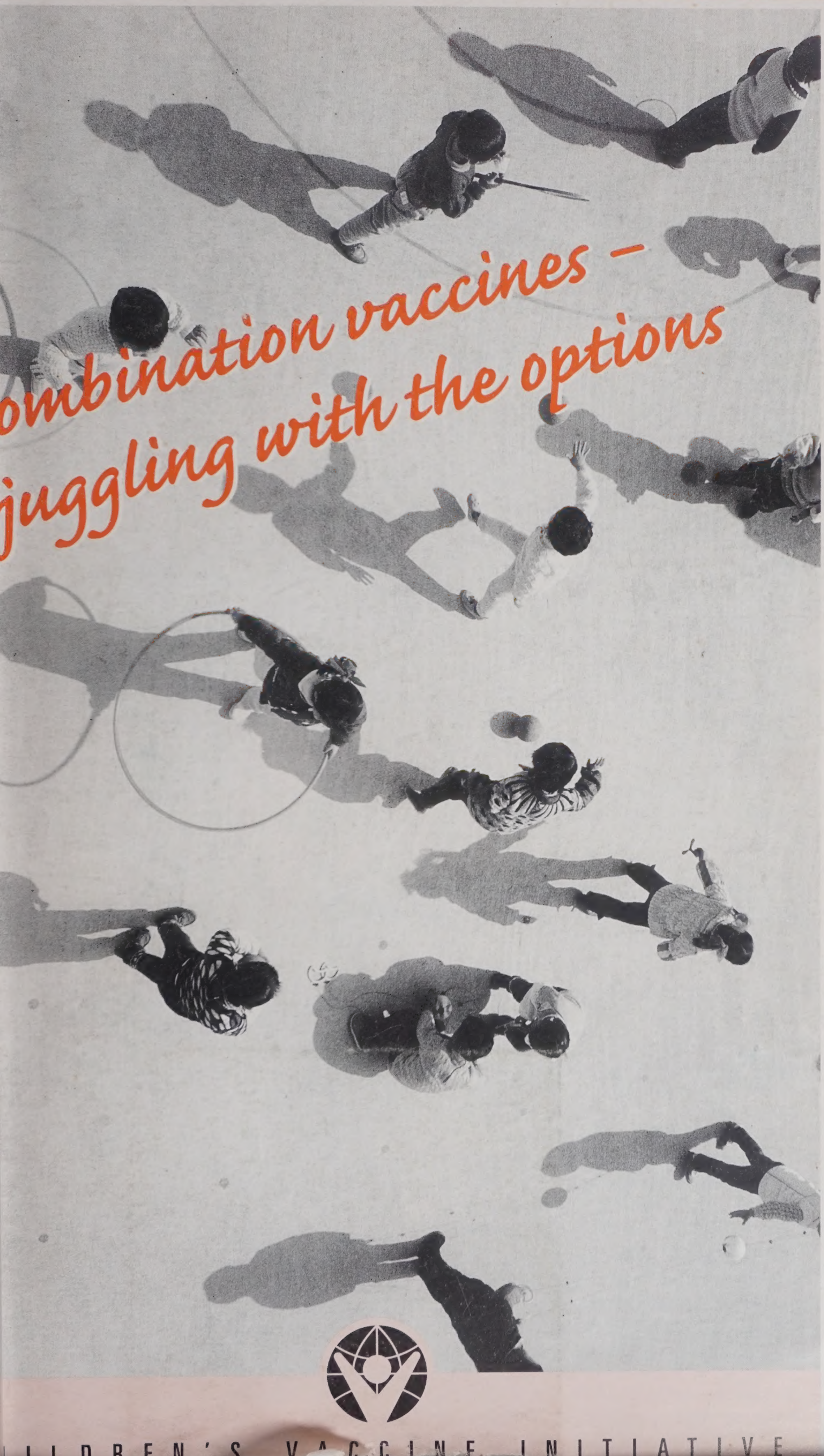

Combination vaccines – juggling with the options

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In this issue

ILDREN'S VACCINE INITIATIVE

A step onwards for the CVI

The Declaration of New York, the founding document of the CVI endorsed by leading development and child health organizations at the time of the World Summit for Children in 1990, called, among other things, for the closest possible collaboration between the WHO and the CVI Secretariat.

Over the years, this collaboration has been implemented both symbolically and physically—symbolically, in the fact that since 1994, at the request of the CVI co-sponsors, I have served as Executive Secretary of the CVI, in addition to being Director of the WHO's Global Programme on Vaccines and Immunization (GPV); and physically, in the housing of the CVI Secretariat within the WHO's offices in Geneva, which has facilitated interaction not just with the GPV but also with other WHO units, including the Biologicals Unit, the Tropical Disease Research Programme (TDR) and the Emerging Diseases Division (EMC).

Over the years, the collaboration has borne fruit, but we should be continually asking ourselves, "Can we do better?"

Today, in my view and in the opinion of many expert observers, the time has come to revisit the relationship. The specific modalities of a new arrangement will be explored in the coming months and widely discussed among the members of the CVI, notably those who will be represented at the CVI's Consultative Group meeting on 9-10 November this year.

There is already, however, a strong consensus that whatever the outcome of those discussions, we should make every effort to work in a more broadly collective mode in future and that, above all, we should preserve the core mission of the CVI, namely, to bring the life-saving benefits of vaccination to all the world's children.

Jong Wook Lee, MD
Executive Secretary, CVI

The Children's Vaccine Initiative (CVI) is a global coalition of organizations from the public, non-governmental and private sectors, including the vaccine industry, working together to maximize protection against infectious diseases through the development and utilization of safe, effective, easy-to-deliver and widely available vaccines. The CVI was launched at the World Summit for Children in 1990 and is cosponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Health Organization (WHO), the World Bank and the Rockefeller Foundation.

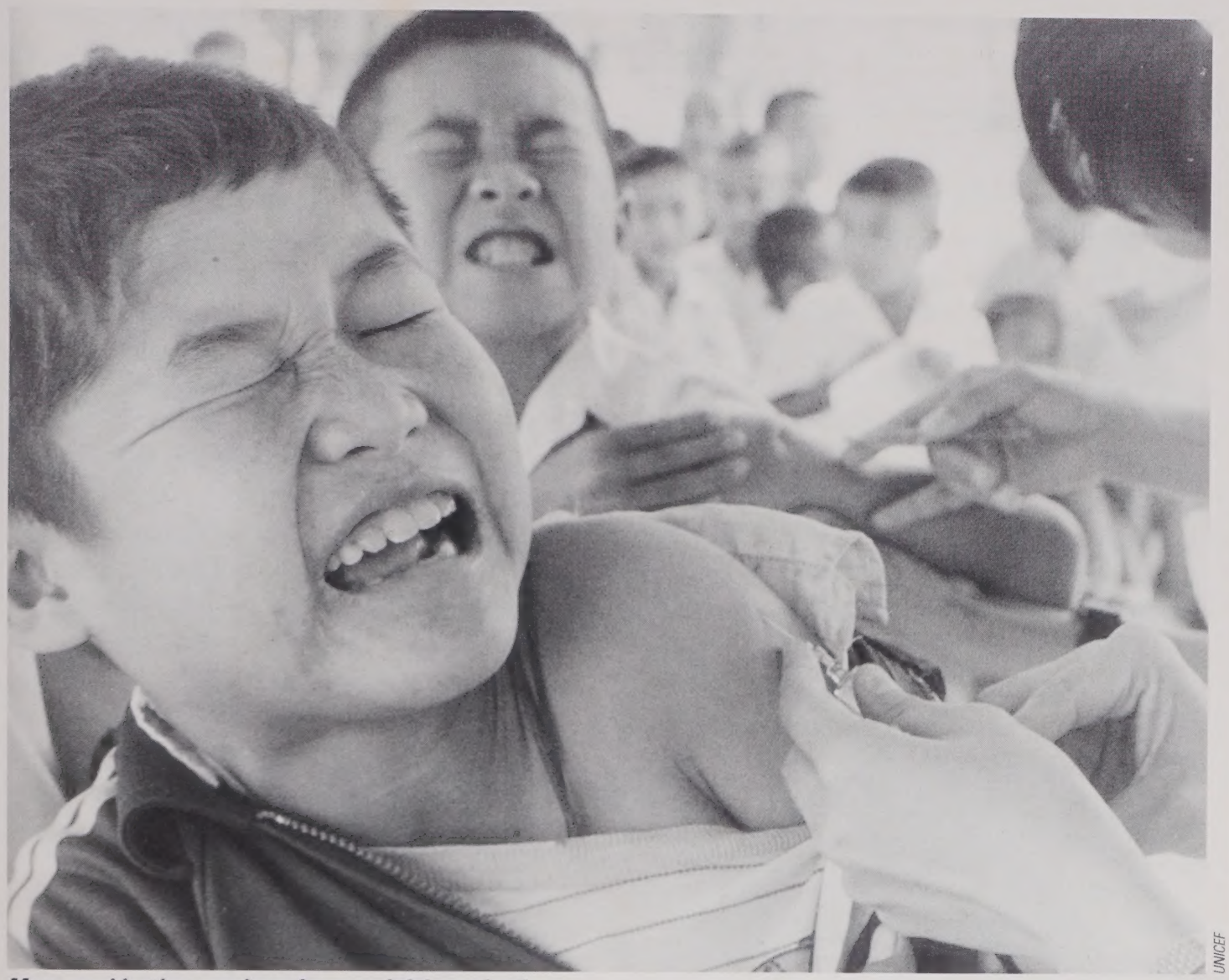
Cover photo:
UNICEF/Roger Lemoyne

Combination conundrums

In the beginning—well, 200 years ago—was the smallpox vaccine. Then, nearly 100 years later, a rabies vaccine was first used in humans, followed in the late 1890s by the first use of vaccines against cholera, typhoid and plague. Then, in the first decade of this century came vaccines against pertussis (whooping cough) and tuberculosis (the BCG vaccine). Since then, in the space of some 80 years, vaccines against another 20 diseases have rolled off the production line.

Of the total 27 diseases, however, all but three—polio, cholera and typhoid—require vaccines administered by injection. To be sure, all children everywhere don't have to be protected against everything. Vaccines against cholera, typhoid and yellow fever, for example, are only needed for those inhabiting or visiting certain parts of the world. But even the standard immunization schedules used today in developing countries call for at least five and often six injections. In the industrialized world, kids have to put up with an impressive battery of shots—14 in the U.S., for example (11 before 18 months of age), more than double the number required ten years ago, with up to four injections in one visit.

And with over 200 vaccines in the research and development pipeline, including new vaccines for infants against pneumococcal and meningococcal disease, the number of injections isn't going to get any smaller. Walter Vandersmissen of SmithKline Beecham Biologicals told a recent CVI meeting[1] that he expects to see a panoply of at least 25 children's vaccines by 2010. In the first ho[illegible] participants



UNICEF

More combination vaccines=fewer painful vaccinations

complained that "we'll soon be running out of kids' limbs." Or, as a U.S. University of Rochester team asked in a report[2] of an opinion survey, "Are children becoming pincushions?"

Interestingly, that survey showed physicians to be more concerned than parents about the number of injections inflicted on children. Nobody seems to have asked the children themselves (not surprisingly, because most of the injections are given to children under 12 months of age). And indeed, the jury is still out about how big a problem multiple jabs really are. Some say they're more of a problem in industrialized than in developing countries. One thing is sure, though, injection is not the safest route of administration.

Combining several vaccines into a single injectable product is one way of limiting the number of vaccine injections. Future technological advances may, of course, produce other solutions, including methods of oral administration, but in the short term at least, as Mr Vandersmissen puts it, "a combination of antigens mixed in a single, convenient product, is a very doable and logical solution to the pincushion problem."

The first crop

It is this logic that spawned the first combinations that appeared between 1949 and 1973:

- 1949—the first multi-pathogen combinations, linking the antigens of diphtheria and pertussis (DP), diphtheria and tetanus (DT) and diphtheria, tetanus and pertussis (DTP);
- 1955—the first multi-strain, single-disease vaccine, the inactivated polio vaccine (IPV, the "Salk" vaccine), which combines the three strains of the polio virus and is administered by injection; and the typhoid-paratyphoid A-paratyphoid B (TAB) vaccine;
- 1957—an adenovirus-influenza combination (shelved in 1980);
- 1958—an oral version of the three-strain polio vaccine, the oral polio vaccine (OPV, or "Sabin" vaccine), which was widely used in the former Soviet Union in 1958 and licensed in the U.S. in 1963;
- 1959—a DTP-IPV combination;
- 1967—a measles-smallpox combination (shelved in 1985, following the eradication of smallpox);

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"A combination of antigens mixed in a single, convenient product, is a very doable and logical solution to the 'pincushion' problem."

"Now with overlapping, non-complementary antigens appearing in different combinations, a sea change has occurred. There's just no way of making the most economical choice intuitively."

- 1970—a rubella-mumps (RuMu) combination;
- 1971—a measles-rubella (MeRu) and a measles-mumps-rubella (MMR) combination;
- 1973—a measles-mumps (MeMu) combination.
- 1975—a vaccine (MenPS) combining two strains (A and C) of the meningococcus (*Neisseria meningitidis*), a cause of meningitis, and using only the bacteria's sugar (polysaccharide) capsules as vaccinating antigens;
- 1977—a polysaccharide pneumococcal vaccine (PnPS) combining 14 "subtypes" or substrains of the pneumococcus (*Streptococcus pneumoniae*), a cause of pneumonia;
- 1981—a second MenPS vaccine combining four strains (A, C, Y and W135) of the meningococcus;
- 1983—a 23-strain PnPS to replace the 14-strain version.

Then in 1990, the CVI appeared on the scene, with a mission, among other things, "to produce and deliver …vaccines, which are simpler to administer." At the first "Consultative Group" meeting of the CVI's partners in December of that year there was much talk of combination vaccines as the most direct route to fulfilling that mission. CVI Coordinator Roy Widdus recalls that "the concept of one or more broadly multi-antigen vaccines ultimately became the major mid-term approach to achieving the CVI goal of simplifying immunization and of raising immunization coverage of children with new antigens as quickly as possible."

Even the hard-nosed vaccine industry was upbeat, if cautiously, with SmithKline Beecham Biologicals Vice-President and Senior Medical Director Francis André talking of a ten-antigen vaccine as "technically feasible." There was also consensus that DTP would be a good first choice as the building block on which to add antigens for introduction into the world's immunization programmes, rapidly and, literally, painlessly. A good choice for two main reasons: DTP was likely to be around for some time, since none of its target diseases are slated for eradication; and DTP, often called the workhorse of the vaccine stable, was and still is the mainstay of national immunization programmes throughout the world (and these programmes were reaching about 75-80% of the world's children under two). In 1991, a new version of DTP, using an "acellular" form of the pertussis vaccine, was licensed in the U.S. Acellular pertussis vaccines, of which the first was developed in Japan nearly 20 years ago, use one or more purified proteins of the pertussis organism (*Bordetella pertussis*), instead of the whole bacterial cell that is used for the traditional "whole-cell" pertussis (wP) vaccine and for the traditional DTP combination (now known as DTwP). DTwP has had a history marred by relatively frequent, although mostly minor, side-effects. DTaP has about the same efficacy as DTwP but fewer side-effects. However, it costs more—about 50% on the U.S. public market, where DTaP has almost completely ousted DTwP — but the price difference is likely to dwindle, if and when DTaP sales volumes increase substantially.

Take your pick

Three years after the 1990 CVI meeting, DTwP made its appearance sporting a Hib antigen (Hib, or *Haemophilus influenzae* type b, is a major cause of meningitis and pneumonia). Today, in some countries, you can also have DTwP combined with hepatitis B (HepB) or with HepB and Hib or with IPV and Hib. Or you can have DTaP with Hib or with Hib and IPV. You can also have an "injection combination" that allows health care providers to use the liquid DTwP-HepB vaccine to reconstitute the lyophilized (freeze-dried) Hib vaccine. You can also have Hib with HepB and HepB with HepA (hepatitis A). So right now, you have a choice of 17 multi-disease combinations (see p. 8).

And there's no reason why, a bit further down the road, we might not eventually see another 17 combinations (see p. 9) bringing to 34 the total number of multi-disease combinations[3].

You're confused? You're not alone. The likely future proliferation of multi-disease vaccines has been called "a recipe for combination vaccine chaos."

To try and bring some order to the impending chaos, a U.S. team of vaccinologists and operations research analysts, including Walter A. Orenstein and Bruce G. Weniger, Director and Assistant Chief for Vaccine Development, respectively, at the National Immunization Programme of the U.S. Centers for Disease Control and Prevention (CDC), have devised what they call "an economic algorithm for vaccine selection."

This algorithm, or problem solving procedure, involves the gathering of data on available vaccines—prices, doses required, vaccine preparation times, cold storage needs, shelf life, frequency of adverse events, protective efficacy, and so on. A computer programme determines which set of vaccines—including combination vaccines—a conscientious physician or immunization programme manager might want to stock to comply most economically with the recommended immunization schedule.

The team ran a pilot demonstration of the algorithm, considering vaccines for only five diseases (diphtheria, tetanus, pertussis, Hib and hepatitis B). To their surprise, the computer came up with 16,000 possible sets of vaccines.

Dr Weniger hopes the algorithm will evolve into a useful tool for health officials, immunization programme managers and health management organizations trying to work out which sets of vaccines offer the best value.

The need for some computer help, Dr Weniger feels, is urgent: "When the DTwP-Hib combination came out, most everyone in the States was using DTwP and Hib vaccines, so the combination was a logical replacement saving one injection. But now with overlapping, non-complementary antigens appearing in different combinations, a sea change has occurred. There's just no way of making the most economical choice intuitively."

The country view

The task is no easier for national immunization policy makers in developing countries. Take an immunization programme manager who is thinking of introducing a new vaccine, say HepB or Hib, and doing so by simply replacing a current vaccine, say DTP, with DTP-HepB or DTP-Hib. Suppose the answer is "yes" to these first questions: Is there a real need for a combination? Is it important to parents in my country that their children be spared extra injections? Are we afraid of unsafe injections? Is the ease of adding a new antigen via the combination likely to outweigh the difficulties and costs of integrating it into my programme and its support system (of vaccine supply, delivery, administration logistics, etc.)?

Then come some trickier questions. Should the programme start by buying DTP-HepB and adding Hib as a second injection or start with DTP-Hib and adding HepB as a second injection? Or should it just use the DTP-HepB-Hib combination injection? And if the immunization programme is in one of the 20 or so developing countries that produce their own DTP, should it jeopardize local production by importing DTP-based combinations? Or should it import the stand-alone vaccines, HepB or Hib or Pn or Men, in bulk, and have them combined with local DTP, which may be less expensive than the imported DTP? Or should it import the Hib-HepB combination and continue using local DTP?

Which raises two more questions.

- Will the local DTP be compatible, chemically and in quality, with the imported antigens? Julie Milstien, scientist with the Vaccine Supply and Quality Unit of the WHO's Global Programme on Vaccines and Immunization (GPV), says that "at least 25% of the world's DTP cannot be said to be of known good quality, [which] raises questions about the feasibility of using locally produced DTP as a basis for combination vaccines."
- Will local DTP production facilities be viable and of high enough standard to entice manufacturers of the newer antigens—most of them in the industrialized world—into the commercial partnerships needed for such arrangements? (GPV experts say that less than a fifth of local vaccine producers in the world are viable—capable, that is, of producing vaccines of demonstrably good quality now and likely to continue doing so in the future?)

While on the subject of DTP, our hypothetical country has another choice to make, namely, between DTwP and DTaP. A few local producers in some countries, such as China and Korea, make acellular pertussis vaccine but most make only DTwP and would have to import the more costly DTaP, if they wanted it. However, at a recent CVI meeting on pertussis[4] several managers of immunization programmes in developing countries said they preferred to stick with the whole-cell version, for cost reasons and, for some of them, because they don't want to damage local DTwP production. A few also expressed doubts about the duration of protective immunity provided by the acellular pertussis component.

Cost is of course a critical consideration. Of the first post-1990 crop of combinations, only DTwP-Hib, DTwP-HepB, HepB-HepA and Hib-HepB carry the relatively new vaccine antigens (HepB and Hib) that have

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Very few developing countries—and most of them are in the middle-income category—have started buying the new combination vaccines.

"We've got the money, the storage space, the political commitment and a motivated community, but I'm stuck without proper information."

been recommended by the WHO for wide use in the developing world. With the exception of DTwP-HebB, which is not licensed yet in the U.S., these combinations sell on the U.S. public market for between $14 and $20 a dose. Manufacturers are offering some of them at prices as low as a tenth of these for the poorest developing countries buying large quantities through UNICEF. But even at the lowest price, a new combination would more than double the $1 or so the poorest countries are spending for all the traditional children's vaccines (DTwP, BCG, polio, measles). Not surprisingly, very few developing countries—and most of them are in the middle-income category—have started buying the new combination vaccines.

For sure, the new combinations will bring savings—in the number of injections and visits to the health centre, for example. They are therefore likely to increase public compliance with immunization, which could push up overall vaccine coverage by a few percentage points. They will also save costs in health worker time, injection equipment, delivery, paper work and other logistical overheads.

There is as yet little or no data to quantify these putative savings, but they will certainly be offset by counter-costs, including an investment in the training of health workers. Vaccine wastage is also a consideration: wastage rates of up to 50% are not unusual for the traditional low-cost vaccines; for a more expensive combination vaccine the cost could be significant and the need to reduce wastage, critical. A possible solution would be to use combinations produced in single-dose vials, but that would make the vaccines more expensive to produce (more vials and vial stoppers, among other things) and may add to vaccine storage and transport costs.

As for developing countries manufacturing their own new combination vaccines, this is possible for some countries with relatively well-established manufacturers: Brazil, China and Indonesia are apparently thinking about making a DTP-Hib or DTP-HepB combination, Korea a measles-Japanese encephalitis combination for sale to the private sector and India a combination of locally produced DTP with imported HepB, to give only a few examples. But most developing countries lack the facilities and technological wherewithal to go this route, at least for the immediate future.

Some developing countries complain about a lack of guidance to help them through the combination complexities. Zimbabwe, for example, is keen to introduce HepB painlessly—by simply replacing its DTP with the DTP-HepB combination. "We've got the money, the storage space, the political commitment and a motivated community, but I'm stuck without proper information," says Adelaide Shearley, manager of Zimbabwe's immunization programme. Ms Shearley wants information about the different combinations currently available—prices, usage in other countries, efficacy, safety and adverse events, compatibility with Zimbabwe's current immunization schedule, the need for booster doses, and so on. "We were supposed to start last August with social mobilization and training of health workers, but I'm still waiting for the information."

WHO/S. YABAO

Few vaccine producers in developing countries have the technical wherewithal to produce the new combination vaccines.

The industry view

For the five major manufacturers of the new combination vaccines—Chiron Vaccines, Merck & Co., Pasteur Mérieux-Connaught, SmithKline Beecham Biologicals and Wyeth-Lederle Vaccines & Pediatrics—these products can pose as many problems as they solve.

The following list is far from complete, but it gives an idea of the kind of challenges facing a manufacturer thinking about its next combination:

Technical challenges

- Will the different antigens in the combination live happily together, even if they are of differing microbial origin (e.g. viral or bacterial) or if some of them are not quite so "pure", i.e. if they contain material beyond what is needed to produce an immune response?
- Will they be immunologically compatible and work in vaccine recipients as safely, consistently and effectively as they do as stand-alone vaccines? (The immune response of infants has been lower to Hib in some versions of the DTaP-Hib combination, for example, than it is to Hib as a stand-alone antigen, suggesting immunological interference between the components of the combination.)
- Will the different chemical additives—preservatives, stabilizers, buffers, salts and so on—that come with the individual vaccines get on well together in a combination product or, as is likely, will costly research have to be done to identify a common set of mutually compatible additives?

Regulatory challenges

- How much preclinical (laboratory and animal) and clinical (human) research must be done to prove to the different regulatory authorities of the different regions of the world that the combination vaccine is of the same quality, stability, safety, tolerability, immunogenicity and efficacy as its individual components?
- How difficult will it be to show protective efficacy for a combination containing the pertussis antigen, since there is no universally accepted test to indicate protective immunity to pertussis?
- If a combination in a clinical trial, or even in subsequent clinical use, causes an adverse effect, how difficult will it be to know which component of the combination was responsible? (The CDC's Dr Orenstein has calculated that it would require a clinical trial involving 31 separate sets of participants, or clinical trial "limbs," to determine the relative contribution of the individual antigens of a five-component combination, if information on partial combinations were lacking.)

The main challenge is from regulatory authorities, who, at least in the U.S. and Europe, regard a combination of existing, already licensed antigens, as a completely new product. "It means," says SmithKline's Mr Vandersmissen, "that we have to begin the whole R&D process from the beginning again. And we could be in for surprises—there's just no cook-book to do it the quick way."

So far, none of the new combinations already in use has shown greater side-effects than the stand-alone vaccines. But going through the whole R&D process could mean an investment of anywhere between $100 million and $200 million, and even higher, most of it on clinical trials.

"Developing a new combination is not quite as expensive as starting from scratch with an individual antigen," says Peter Paradiso, Vice-President for Scientific Affairs and Research Strategy at Wyeth-Lederle Vaccines & Pediatrics (WLVP). "But the regulatory requirements for combinations are now as rigorous as for an individual new component. The difference is that instead of having to do the large-scale efficacy trial needed for an individual component, you have to do large-scale comparative trials to prove the combination is as effective as its individual components. The outcome of such trials is easier to measure, so the process takes less time, but it's a lot of work. We're not very far from the level of funding needed to develop a new vaccine."

The licensing process alone can mean a multi-million dollar outlay, partly because manufacturers have to prepare different product application files for different regulatory bodies: efforts are under way (notably by an International Conference on Harmonization, comprising government officials and manufacturers from Europe, Japan and U.S., and also by the CVI) to bring the world's multiple regulatory requirements into some kind of global harmony. Progress has been made, but there's still a long way to go for complete harmonization.

"Developing a new combination is not quite as expensive as starting from scratch with an individual antigen. But the regulatory requirements for combinations are now as rigorous as for an individual new component."

Combin

Available now

HepA-HepB

Hib-HepB

DP

DTaP-Hib-IPV

DT

DTaP-Hib

DTwP

DTwP-Hib-IPV

DTaP

DTwP-HepB-Hi

DTwP-IPV

DTwP-HepB

Ru-Mu

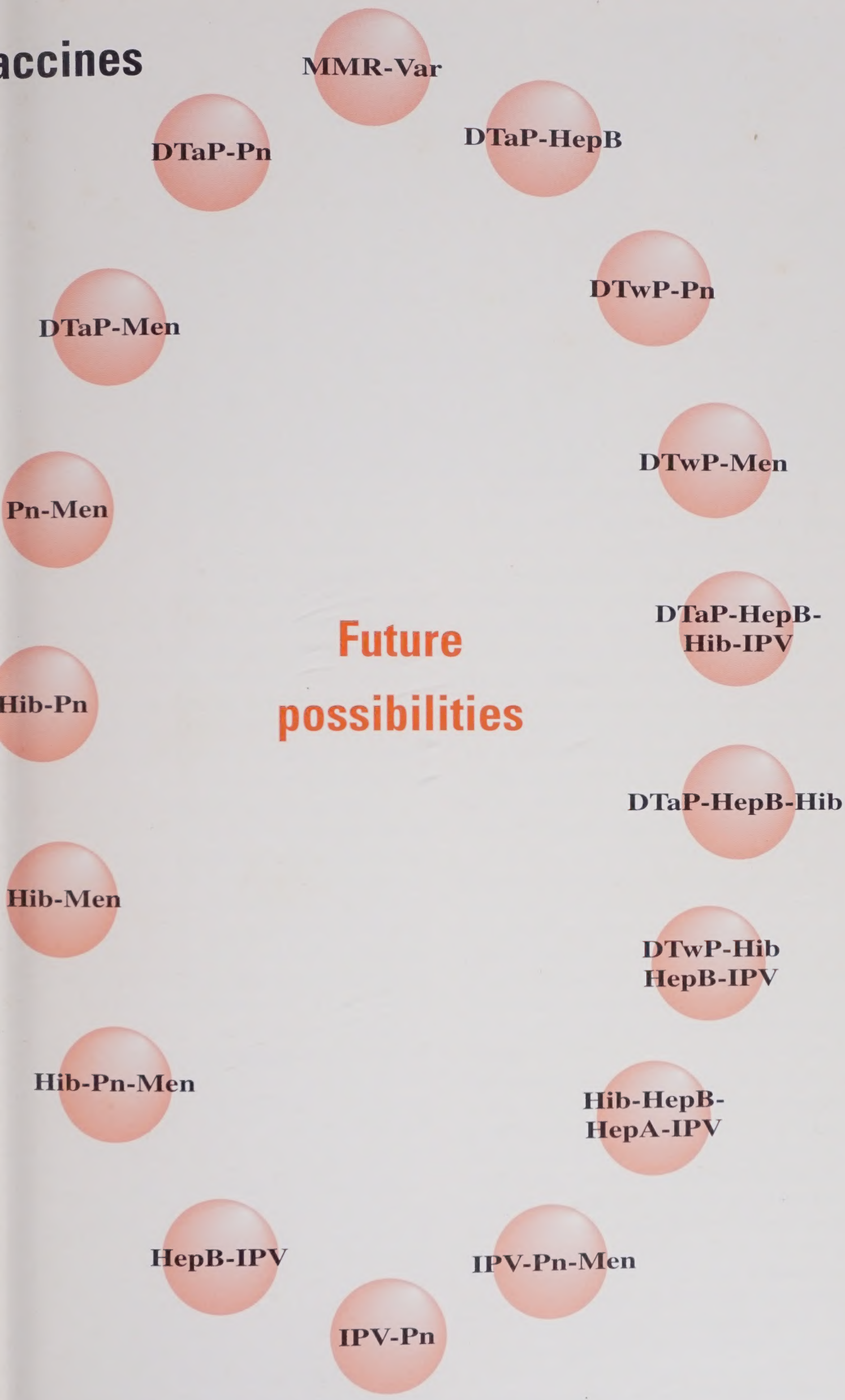
DTwP-Hib

Me-Ru

Me-Mu

MMR

DP	diphtheria-pertussis
DT	diphtheria-tetanus
DTaP	diphtheria-tetanus-acellular-pertussis
DTwP	diphtheria-tetanus-whole-cell-pertussis
HepA	hepatitis A
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
IPV	inactivated polio vaccine
Me	measles
Men	meningococcus
MMR	measles-mumps-rubella
Mu	mumps
Pn	pneumococcus
Ru	rubella
Var	varicella


accines
MMR-Var
DTaP-Pn
DTaP-HepB
DTaP-Men
DTwP-Pn
DTwP-Men
Pn-Men
Future
possibilities
DTaP-HepB-
Hib-IPV
Hib-Pn
DTaP-HepB-Hib
Hib-Men
DTwP-Hib
HepB-IPV
Hib-Pn-Men
Hib-HepB-
HepA-IPV
HepB-IPV
IPV-Pn-Men
IPV-Pn

"You start off with a market for your individual components. You know that with time, the competition is going to combine their individual components and take away your market. So, if you don't do the same, you'll lose that market."

Marketing challenges

- Should a manufacturer plan his combination portfolio to meet the needs of the industrialized or of the developing world or both? And if both, which combinations, if any, would capture a global market?
- Does the manufacturer have easy access to the desired antigens or, as is more likely, must he acquire them through a relatively costly process of partnerships, intellectual property right agreements, joint ventures or other arrangements?
- Will these arrangements accelerate the consolidation of the industry into mammoth "corporate combinations" (most of the vaccine market is now shared by only five companies)?
- Will such a consolidation process lead to companies having a monopoly of certain combinations and of abusing that monopoly to control certain markets?
- How long will a new combination survive in a market where successive combinations, with possibly longer "strings" of antigens, are likely to supersede it relatively quickly?
- If, as is likely, a combination's life cycle will be short, particularly in the industrialized world, will it have a large enough market for a long enough time to justify the large production volumes needed to ensure an adequate return on investment? If not, will its market support a price high enough to achieve the same purpose?

Each of these challenges adds an element of risk to the development of combinations. Understandably, their cumulative effect—plus the lack of guidance from public health agencies as to the most useful combinations—has somewhat eroded the industry's early enthusiasm and optimism for these products.

Dr Paradiso agrees that combinations have not quite lived up to expectations, but wonders "if it's because the expectations were set too high or if there have been real difficulties." Certainly, he admits, there have been technical problems, such as interference between Hib and DTaP. But otherwise, "most of the new combinations have been successfully done. What's happened is that the market situation has changed, at least in the industrialized countries. With HepB being more widely used in infants, with aP more or less replacing wP in DTP and with IPV replacing much of the oral polio vaccine, the needs of the population have changed."

Nevertheless, the combination market has a good deal of uncertainty about it. Uncertainty may have merits for physicists but is anathema to businessmen, especially when relatively large capital investments are at stake.

Much of the uncertainty stems from the unpredictable magnitude of the technical and regulatory problems that a new combination could encounter. Many people thought initially that combinations would be relatively easy things to put together—an antigen or two here, an adjuvant and stabilizer there, and off you go. It has not been so easy, and surmounting every difficulty, every challenge, has meant unanticipated costs. Even DTaP has not quite lived up to its expectations: it does have a comparative advantage over DTwP, at least in producing fewer minor reactions, but not to the extent that would enable it to readily overcome the hesitancy of markets in developing countries (and to some extent also in industrialized countries). For this and other reasons mentioned earlier, those markets have generally been less avid for the new combinations than was originally anticipated.

With all the diminished hopes and the hurdles and complexities and risks, one wonders why the vaccine industry is plunging ahead with the development of even newer, more complex, more risky combinations.

Commercial interest, for one thing. Despite all the constraints, the market for combination vaccines is, according to some analysts, a buoyant one with a rosy future. Healthcare research analyst Akmal Bhatti of the British consulting firm Frost & Sullivan says global revenues from combination vaccines have risen steadily from $1.2 billion in 1992 to $1.7 billion last year, a 48% increase. Between now and 2002 they are, he believes, likely to more than double, to $3.8 billion. Sales of combination vaccines, according to Frost & Sullivan estimates, will have accounted for 40-50% of the total vaccine market over this ten-year period.

Combination vaccines offer other advantages to manufacturers. They can restore market vigour to a flagging, low-price or generic stand-alone vaccine by incorporating it into a new, premium-priced multi-antigen product. Or conversely, an attractive stand-alone vaccine can do the same for an old low-priced combination, like DTwP. Or DTwP can be added, at little or no extra cost, to a new vaccine struggling for a share of the market.

UNICEF/Betty Press

To make the right decisions among a maze of options, immunization programmes in developing countries need more information about new combinations.

Dr Paradiso explains: "You start off with a market for your individual components. You know that with time, the competition is going to combine their individual components and take away your market. So, if you don't do the same, you'll lose that market."

Luis Barreto, Director of International Public Health Affairs at Pasteur Mérieux-Connaught, adds: "Our motivation over the past ten years has also been the desire to develop our strategic position in certain countries. The challenge, however, is to know where and how to introduce the new combinations in those countries and to monitor their impact on local disease patterns. It is also important to do this hand-in-hand with the public health officials of the countries and with guidance from the international organizations."

The public sector view

International health organizations look nostalgically back to the 1970s and 1980s, when they could, rightly or wrongly, recommend to all countries a single, simple, easily understood basic package of vaccines corresponding to the needs of all children in the world and delivered in each country through a standard immunization programme.

But today, things aren't so simple. As Dr Widdus puts it: "Nowadays, there are more vaccines on the market and more diseases preventable by vaccines. So a country wishing to use its resources rationally can and indeed must choose a menu of vaccines that corresponds to its needs and to the particular diseases it wants to prevent."

The advent of new combinations, which allow for even more finely tuned choices, has hastened the demise of global solutions and intensified the need for individual solutions. The WHO has recommended several new vaccines, notably HepB and Hib, but, as Dr Widdus notes, "more and more countries seem to be seeking more customized guidance and often request cost-effectiveness studies."

Dr Paradiso welcomes the fact that "a lot of groups, including the WHO and the World Bank, realize that we all have to come up with some novel ways of financing, if we manufacturers are to start producing hundreds of millions of doses of some of these new vaccines, including the new combinations. Which is something we're not prepared to do under the current ten-cent-a-dose paradigm."

Manufacturers too need guidance about the potential market for this or that mix of antigens in a future combination product. The WHO, the CVI Secretariat and other organizations are trying to gather the kind of information—about the burden of certain childhood diseases, for example, or the prevalence of certain strains of pathogens in specific countries or areas of the world—that could help manufacturers. But there are problems. "Take a Hib-Pn combination," says Dr Widdus. "A logical next addition would be a meningococcal antigen. But which strain? Meningococcal A, which is the

"Nowadays, there are more vaccines on the market and more diseases preventable by vaccines. So a country wishing to use its resources rationally can and indeed must choose a menu of vaccines that corresponds to its needs and to the particular diseases it wants to prevent."

OMS/Nt Crozet

Gro Harlem Bruntland, the WHO's new Director-General, talks to the press. Public health bodies, including the WHO, don't have an easy time providing guidance needed by countries and vaccine manufacturers on combination vaccine options.

"There has to be an epidemiological justification for sticking a given antigen onto a combination. It can't be determined simply by fad or fashion."

predominant strain in some countries? Or C or B, which are the big problems in others? Or A, B and C together?"

Another example of a global-vs.-local antinomy is the DTP-HepB combination. Most countries could use the DTP-HepB combination at six, ten and fourteen weeks (the regular DTP schedule). In Asia, however, up to a third of people carrying the hepatitis B virus are infected during childbirth and such mother-to-baby transmission can be prevented by giving the first dose of HepB at birth. Countries with this type of viral spread would also need to keep a stock of "monovalent" (or stand-alone) HepB for birth doses.

In the end, free market forces may determine how the combination complexities pan out. But allowing the market to decide has its pitfalls. "There has to be an epidemiological justification for sticking a given antigen onto a combination," says David Salisbury, Principal Medical Officer in the United Kingdom's Department of Health. "It can't be determined simply by fad or fashion." Mr Vandersmissen agrees: "There must be a minimum of logic. But for us, in the industry, part of that logic is catering for the comfort of vaccine recipients. You could say mumps or varicella is not such a terrible disease. But adding either antigen to a combination could make the whole product more attractive to the public."

For a public health entity like the CVI, the logic is, as Dr Widdus says, "the need to move at some point in time from stand-alone vaccines to combinations simply to avoid multiple injections."

One direction in which combinations are moving is towards so-called syndromic vaccines against groups of related diseases. Already human trials suggest the feasibility of combining a typhoid and cholera vaccine. Adding rotavirus, *Shigella* and *Escherichia coli* might prove technically difficult but would, as Dr Widdus says, "provide an absolutely ideal diarrhoeal disease vaccine for travellers to and residents of countries where such diseases are endemic." Clinical trials are also starting for a combination vaccine against pneumococcal, meningococcal and Hib diseases.

* * *

Guidance as to the way combinations should go may be forthcoming one day. CVI Executive Secretary and GPV Director Jong Wook Lee hopes it will be soon: "We have to work closely and efficiently with all the partners in the vaccine community in order to provide the guidance and information that countries, manufacturers and the community as a whole need in order to plan for the future. Without such guidance, combination chaos is inevitable."

Notes

1 Setting the agenda for the introduction of combination vaccines, 23 April, 1998, Geneva.

2 Kathleen A. Woodin *et al.*, *Archives of Pediatrics & Adolescent Medicine*, August 1995, Volume 149.

3 Adapted from B.G.Weniger *et al.* Addressing the Challenges to Immunization Practice with an Economic Algorithm for Vaccine Selection, *Vaccine* 1998;16, in press.

4 Pertussis control and pertussis vaccines, 18-20 May, 1998, Geneva.

Hib—who's using it, who isn't and why not?

The first "modern" vaccine against the bacterium *Haemophilus influenzae* type b (Hib)—a major cause of often fatal meningitis and pneumonia—appeared on the scene about a decade ago. This so-called Hib *conjugate* vaccine, unlike its unconjugated predecessor, can protect infants under two years of age and not just older children and adults. At this writing, 34 countries or territories have adopted the Hib conjugate vaccine into their routine childhood immunization programmes. Nineteen of them are industrialized and 15 developing. A further two countries in Latin America are using the vaccine in parts of their populations. A further 12 countries—three industrialized and nine developing—are considering adopting the vaccine in the next 18-24 months. The industrialized countries as a whole got off to a relatively early start: as a result, Hib disease has now been virtually wiped out in the U.S., Western Europe and Australasia.

Of the 15 developing countries or territories using the vaccine routinely, one is a grouping of Pacific island nations. All but two are in the middle- or upper-middle-income category: of the two exceptions, Kuwait is in a high-income category and Gambia in a low-income category (but gets its Hib vaccine through a donation[1]). In addition, unknown quantities of the Hib vaccine are being administered to children in an unknown number of countries through private health care (in Lebanon, for example, 90% of all vaccine doses are given through the private sector).

Be that as it may. Today, 181 (84%) of the 215 countries and territories reporting to the WHO are still not using the Hib vaccine in their national immunization programmes. So Hib disease still occurs in many parts of the world, especially in developing countries, where it is causing at least 3 million cases of severe disease and 400,000-600,000 deaths annually.

Why the delay in wider adoption of the vaccine?

Are there doubts about the safety or quality of the vaccine in developing countries? In a recently published "position paper[2]" the WHO notes that "no serious side-effects are recorded" and that "the Hib vaccine may safely be administered concurrently with any vaccine [commonly used…] in national childhood vaccination programmes." What's more, all commercially available Hib vaccines are, according to the WHO, "of known good quality."

Is there any doubt about the vaccine's efficacy? Wherever the vaccine has been widely deployed, it has brought cases of Hib disease down to negligible levels—and that includes at least three developing countries that have monitored the vaccine's impact:

- In Uruguay, annual cases of Hib disease in infants fell by over 95% within two years of introduction of the Hib vaccine in 1994.
- In a Gambian study, the vaccine not only reduced by 95% the risk of invasive Hib disease among children but also cut X-ray confirmed pneumonia from all causes by 20%. Moreover, it reduced asymptomatic "carriage" of the Hib organism by 60% in vaccinated children, suggesting (but not proving) that the vaccine might, through an overall reduction in the spread of Hib infection in a community (a so-called "herd" effect), protect even unvaccinated children in the community.
- In Chile, in a trial involving 39,000 infants, the vaccine reduced the risk of invasive Hib disease by 90%.

In industrialized countries, trials in over 200,000 children in Finland and the U.S. have given similar rates of protection. In the U.S., in particular, the vaccine reduced the incidence of Hib diseases by 98% and virtually wiped out asymptomatic carriage of the organism.

Are countries waiting for an official international recommendation? The Scientific Advisory Group of Experts (SAGE) that counsels the CVI and the WHO's Global Programme for Vaccines and Immunization (GPV) has urged adoption of the Hib vaccine

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in the routine infant immunization programmes of countries "as appropriate to national capacities and priorities": in other words, of countries that need the vaccine and believe it is worth paying for.

Is the Hib vaccine cost-effective? Worldwide, CVI analyst Mark Miller calculates that the Hib vaccine, used routinely and reaching roughly the same proportion of children as other routinely used vaccines, could prevent about 70% of the estimated 400,000 deaths from Hib disease that are occurring annually and could do so at a global average cost of $3,642 per death prevented. For the poorer developing countries in the WHO's African, Eastern Mediterranean and South-East Asian regions, where about 80% of the deaths occur, this cost would range from $1,116 to $1,510. To run Hib vaccine programmes in all the countries of these regions that have a gross domestic product (GDP) under $2,555 *and* a high prevalence rate for Hib disease would cost a total of $338 million annually (vs. a global total of $1.05 billion) and would save in treatment costs a total of $119 million annually (vs. $402 million globally). The cost per year of life saved in these countries thanks to these Hib programmes would range from $14 to $20 (vs. a global average of $46). "Based on criteria used by financial bodies such as the World Bank," says Dr Miller, "the Hib vaccine would therefore be an extremely good buy for these countries."[3]

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Is the vaccine difficult to use in the field? On the contrary, the three licensed versions of the vaccine come in liquid or lyophilized (freeze-dried powder) form, in single- or multiple-dose vials and can be administered separately or in the same syringe as the diphtheria-tetanus-pertussis (DTP) combination vaccine. To make life even easier, there are also a DTP-Hib and a DTP-Hib-hepatitis B combination on the market. The recommended full three-dose regimen for Hib, moreover, corresponds to the routine DTP dosage schedules (6, 10 and 14 weeks of age), so no extra contacts or visits are needed. On the other hand, a CVI survey of four developing countries that have recently adopted the Hib vaccine showed that some health officials find the array of possibilities offered by the different formulations of the vaccine confusing.

"Do most developing countries need the vaccine?" The chances are many of them do. Wherever the burden of Hib disease has been studied, this organism has been shown to be the commonest cause of bacterial meningitis and the second commonest cause (after *Streptococcus pneumoniae*) of acute bacterial pneumonia—the big child killer in many developing countries. The trouble is, precise data on the burden of Hib disease have been obtained from very few developing countries, outside of Chile in the Americas, Kuwait and Qatar in the Eastern Mediterranean, and the Gambia, Niger, Senegal and South Africa in Africa. Most developing countries, particularly in Asia and Eastern Europe, don't know just how big a Hib problem they have.

To fill that gap, scientists, international agencies and vaccine manufacturers have got together, with encouragement, coordination or financial backing from the CVI and the GPV's Vaccine Research and Development Unit, to map the extent of Hib damage in as many different places as possible around the globe[4].

In the Americas, for example, a system of surveillance of Hib disease is being or has been set up with help from the Pan American Health Organization (PAHO) in 12 Latin American countries, notably, Argentina, Chile, Colombia, Costa Rica and Uruguay, where the vaccine is already in routine use; in Brazil, Mexico and Peru, where it is being used in parts of the population; and in the Dominican Republic, El Salvador, Guatemala and Nicaragua, where it is not yet in use. Studies to measure Hib disease burden are also already under way or being planned in Asia, Eastern Europe and Africa.

"OK, we have a Hib problem. What will it cost to solve it?" Price, as the CVI survey suggested, may well be the biggest obstacle to the vaccine's adoption. Manufacturers, who sell the vaccine for $15-17 a dose on the U.S. private sector market and for $5-7 to the U.S. public sector, are offering the vaccine at about $3 to developing countries. All the standard vaccines (DTP, measles, polio, tuberculosis) put together cost little more than $1 for the neediest countries buying through UNICEF: so even at $3 a dose, the Hib vaccine is seen as too expensive by many developing countries.

This problem, too, is being tackled. Several studies have explored the possibility of cutting costs by reducing the dose or numbers of doses of the Hib vaccine needed for adequate protection. One study in South Africa showed a 1µg formulation to be as immune-stimulating (*immunogenic*) as the normal 15 µg formulation. Another, in

Indonesia, found a quarter-dose formulation of the DTP-Hib combination just as immunogenic as a full-dose formulation. And a third study, in Chile, found no lowering of protective antibody levels in children given three half- or third-doses or even two doses of the Hib vaccine instead of the usual three full doses. So, reducing the number or size of doses may be an option, although potential problems of administration and safety have still to be carefully assessed. Moreover, industry officials have pointed out that reducing the amount of antigen in the vaccine may in the end have little effect on its price and that the results of dose-reducing studies conducted under well-supervised, sanitized conditions may not translate into a real advantage in rough'n tough field conditions.

Another approach to the cost problem is to find novel ways of helping countries acquire the necessary funds. One way currently being explored is for countries to use loans, obtained at very low interest rates from development banks, such as the World Bank, for vaccine purchases.

* * *

One thing is sure: a whole crop of new vaccines is in the offing—against rotavirus and pneumococcus in the near future, and respiratory syncytial virus further down the road, to mention only three. These new vaccines are likely to encounter much the same obstacles as the Hib vaccine is facing. Current efforts by the CVI and other groups to overcome the obstacles, therefore, could well have a trailblazing impact.

Notes

1 In an arrangement brokered by UNICEF and the WHO, the vaccine manufacturer Pasteur Mérieux-Connaught last year agreed to provide enough doses of Hib vaccine to cover the needs of the Gambia's immunization programme for five years.

2 *Weekly Epidemiological Record,* 73, 64-71, 1998 (6 March).

3 These estimates are based on Dr Miller's vaccine policy analysis method (see *CVI FORUM* No. 15, February 1998, pages 9-10). The results of the method are usually expressed as ranges and not, as here, as "point estimates" or single figures. Ranges more accurately reflect the wide variability in the geographical, economic and epidemiological circumstances of countries.

4 Epidemiologists, backed by the GPV's Vaccine Research and Development Unit (VRD), are using or will use a "generic protocol" developed by the VRD to measure Hib disease burden in Guatemala, Dominican Republic, Bulgaria, Poland, India and the Newly Independent States. Studies planned in East Asia are part of a project conducted by the International Vaccine Institute in Seoul, Korea, and backed by the United States Agency for International Development (USAID, through the CVI) and Hib vaccine manufacturers, including Chiron Vaccines, Merck & Co., Pasteur Mérieux-Connaught, SmithKline Biologicals and Wyeth-Lederle Vaccines & Pediatrics. The Program for Appropriate Technology in Health (PATH) and the Association for Preventive Medicine (AMP) are backing a study in Indonesia, as is the Philippines' National Public Health Institute (NPHI) in the Philippines.

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欢迎我们的中国读者

Welcome to our Chinese readers

A Chinese edition of the *CVI FORUM* will be available starting with this issue. It will be prepared and distributed by the Institute of Medical Information of the Chinese Academy of Sciences in Beijing, with support from SmithKline Beecham.

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Who's next on the eradication hit list?

With polio and Guinea worm disease (dracunculiasis) headed for the history books, disease eradication is in vogue. In the last year, two major meetings have discussed the topic. In March 1997, a workshop in Berlin addressed the science of disease eradication. And in February, a follow-up conference organized in Atlanta by the Task Force for Child Survival and Development, thrashed out thorny public health issues, including the debate between "horizontalist" defenders of routine health systems and "verticalist" proponents of eradication. The Atlanta meeting, which was attended by 200 people representing 81 organizations from 34 countries, covered five areas. A sampling of its conclusions:

❍ *Sustainable health development:* Tensions between eradication and sustainable health development are inevitable because of the polarization between the specific, time-limited goals of the one and the comprehensive, long-term goals of the other. Eradication programmes should aim not only to eradicate the target disease but also to strengthen and further develop health systems. The resources they use should be additional to those available for basic health care services. Enhanced leadership, managerial skills and top-level disease surveillance systems are possible spin-offs of eradication efforts that can benefit basic health services.

❍ *Non-infectious diseases:* Micronutrient deficiencies, lead intoxication and silicoses could be better controlled but are not eradicable.

❍ *Bacterial diseases: Haemophilus influenzae* type b (a major cause of meningitis and pneumonia) and, in the longer term, tuberculosis could be future candidates for eradication, but much research needs to be done first. "Aggressive action" is needed to improve the control of other bacterial diseases.

❍ *Parasitic diseases:* Beyond Guinea worm disease, no other parasitic diseases are current candidates for eradication. However, potent, long-acting drugs are now available, which might eventually make possible the eradication of river blindness (onchocerciasis) and most forms of lymphatic filariasis.

❍ *Viral diseases:* Measles and rubella could become eradication targets in the next 10-15 years. Industrialized countries should move now towards eradication of measles. Developing countries should move more gradually, to avoid undermining the current polio eradication effort and, for some of them, to bring their immunization capacity up to the necessary level. Eradication of rubella as an add-on to measles eradication is biologically feasible, but the burden of rubella, its practical feasibility and the cost of adding it to a measles eradication effort need to be evaluated.

Walter Dowdle, Director of Programmes with the Task Force, and chief organizer of the Atlanta conference, believes eradication is "a natural, almost inevitable end-product of control—provided, of course, the disease is eradicable." But the meeting showed, he said, that "at any given time it is almost impossible to predict what diseases to target next for eradication. The decision depends on the tools available, on the doability of the task and on the goals of the period—all things that change with time."

CVI Coordinator Roy Widdus found the meeting "refreshingly balanced." "Many people," he said, "feared it would endorse a headlong rush to eradication. But in fact, it gave strong emphasis to the need, especially in Africa, for strengthening routine health services and immunization programmes before any new eradication initiatives were undertaken." One outcome of the meeting, he added, was "the recognition that eradication can be a powerful public health tool but can sometimes produce surprises, including unanticipated difficulties, and should not be undertaken lightly."

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